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BOSTON UNIVERSITY

GRADUATE SCHOOL

THESIS

THE USE OF DIISOPROPYL ETHER AS A SOLVENT IN THE GRIGNARD REACTION

by

Gerald Mangan Davis

B.S. Northeastern University 1934

Submitted in partial fulfillment of the

requirements for the degree of

Master of Arts

1935

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I. INTRODUCTION.

This research problem was undertaken to discover whether it would be advisable to substitute diisopropyl ether for diethyl ether as a solvent in the Grignard Reaction and, if it is at all suitable, to determine the optimum conditions. A study of the literature shows that solvents other than diethyl ether have been used, principally benzene, dimethylaniline, gasoline, and toluene, but no mention was made of diisopropyl ether. If the results of the research prove that diisopropyl ether can be substituted for diethyl ether a saving can be realized, for diisopropyl ether is much more inexpensive, as it is made from diisopropyl alcohol which is prepared from propylene, a by-product in the cracking of petroleum.

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II. LITERATURE OF THE GRIGNARD REAGENT.

A. The Grignard Reagent and its formation.

In the year 1900 Grignard discovered that anhydrous methyl iodide and magnesium reacted when mixed in anhydrous ether. He found that most of the magnesium dissolved leaving only a small residue probably consisting of impurities in the magnesium[4]. The solution which Grignard made, when treated with water, evolved methane, and when treated with a compound containing a carbonyl group formed an alcohol on hydrolysis. This is a characteristic property of all compounds made under the same conditions as used by Grignard and have come to be known as Grignard Reagents.

Certain conditions have to be observed in preparing Grignard Reagents. No halide must be used which will react with the compound formed. Bromoacetone could not be used as a reagent in preparing Grignard Reagent because the carbonyl group of the bromoacetone would react with the magnesium halide compound formed. Ordinarily the simple halides of bromine and iodine are used. It has been noted[7] that the heavier the molecule of the halide

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the harder it is to start the reaction. Methyl bromide or methyl iodide will start reacting almost immediately when mixed with magnesium and ether while n-hexyl bromide when treated under similar conditions requires the addition of heat to start the reaction and to keep it going. The yield in this case is very low. The reason advanced for the low yield, in the case of high molecular weight halides is the secondary reaction which takes place. It is assumed that a molecule of aryl or alkyl magnesium halide is formed and if there is an excess of the halide present this reacts with the R-magnesium halide and forms the hydrocarbon. Thus:

$$RX + Mg \longrightarrow RMgX$$

$$RMgX + RX \longrightarrow R\text{-}R + MgX_2$$

In order to reduce this secondary reaction to a minimum it is advisable to allow the halide to flow in drop by drop so that at no time will there be a great excess present to react with the R-magnesium halide.

As a rule chlorides are not used because they are so unreactive. However, Gilman[7] has devised a method for using chlorides by heating the chloride and magnesium in a sealed tube at 150° - 160° C. in the absence of any solvent.

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The yield obtained when phenyl chloride is used is 85% phenyl magnesium chloride and some p-diphenyl magnesium chloride.

It has been found that the alkyl halides[7] react much more readily than the aryl halides. Gilman also found that the alkyl halides from primary alcohols gave much better yields than the halides from secondary alcohols which in turn gave better yields than the halides of tertiary alcohols.

B. Reactions of the Grignard Reagent Involved in this Thesis.

1. Preparation of Saturated Hydrocarbons.

After the Grignard Reagent has been formed, if water is added there is a vigorous reaction and a hydrocarbon is formed.

$$RMgX + HOH \longrightarrow R\text{-}H + Mg(OH)X$$

Alcohols, phenols, oximes, and acids all have the power to produce similar decomposition with the formation of a hydrocarbon.

A genaral rule for the formation of hydrocarbons, is that the Grignard will yield hydrocarbons with most substances containing a hydrocarbon attached to an acid forming element.

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2. Preparation of Tertiary Alcohols.

Tertiary alcohols are formed when Grignard Reagent and an ester, ketone, acid chloride or acid anhydride react and are hydrolyzed. When a ketone is used one molecule of Grignard's Reagent is necessary while for the other reagents two molecules are needed.

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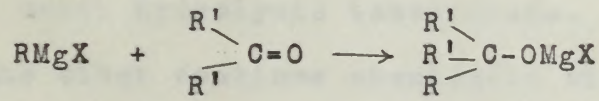

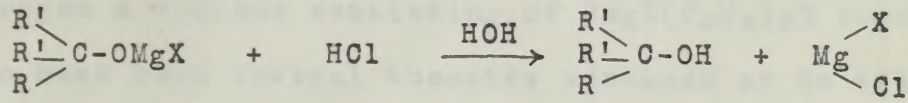

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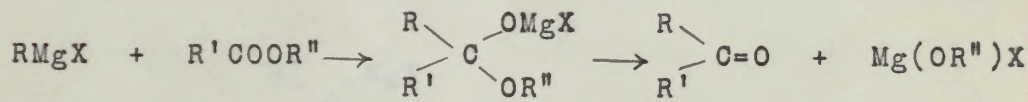

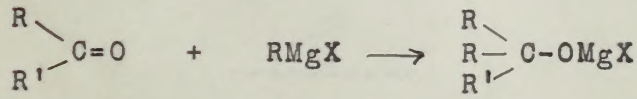

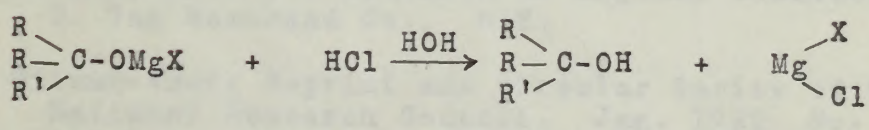

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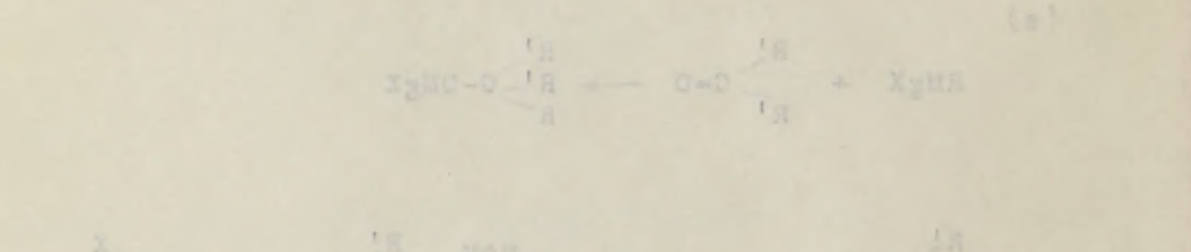

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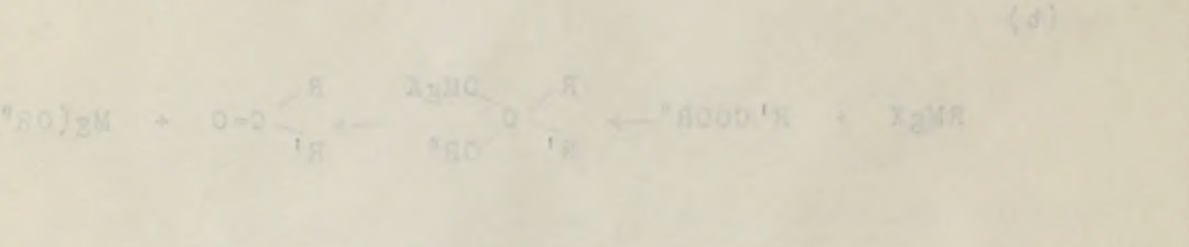

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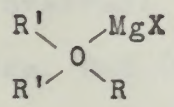
When Grignard first noted the reaction between methyl iodide and magnesium in ether he concluded that the product formed was a simple compound methyl magnesium iodide, but investigation showed that this is only true when solvents other than diethyl ether are used. When diethyl ether is used the ether is loosely held by the organo-magnesium halide until hydrolysis takes place. It has been shown[1] that the ether combines chemically with the organo-magnesium halide for if it is heated in vacuo in a stream of hydrogen a residue consisting of $RMgI(C_2H_5)_2O$ remains.

There have been several theories advanced as to the structure of these compounds. Grignard[4] believed at first that the ether was held as ether of crystallization, but later presented the formula for the compound as being:



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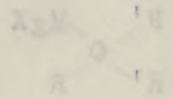

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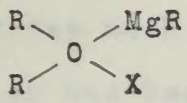

Work by Thorpe and Kamm favors the acceptance of Baeyer's formula for they reason if Grignard's formula were true the decomposition products should be two different hydrocarbons when the etheral substance was treated with dilute acid and the ratio of the hydrocarbons should be equal, but this was not found to be the case.

Tschelinzeff has found that the Grignard complex crystallizes from its ether solution with two molecules of ether of crystallization. From his study of the heat evolved by the combination of magnesium complexes with ether he is led to the conclusion that there are two distinct processes involved: (1) the formation of the magnesium alkyl halide, and (2) the combination of these substances with ether.

D. Use of Solvents other than Diethyl Ether.

Experiments have been carried out using solvents other than diethyl ether and in all cases it was shown that the use of other solvents greatly reduced the yields.

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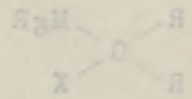

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The influence of solvents in preparing Grignard Reagents was studied by Gilman and McCracken[3] and they found that the yield using diethyl ether was much greater than when benzene, toluene, or petroleum ether had been used. In these experiments a little diethyl ether had been added to start the reaction and then the other solvent was added.

In the preparation of n-pentane[6], dibutyl ether is generally used without a great loss in yield. This ether is recommended because of its high boiling point. If diethyl ether were used it would be difficult to separate the n-pentane from it because of the closeness in boiling points. C.S. Marvel, A.T. Blomquist, and L.E. Vaughn[7] recommend the use of this ether when the boiling point of the product is fairly close to that of diethyl ether.

Chelinzew[4] has used benzene as a solvent in preparing Grignard Reagents and has found that the yields were much smaller than when diethyl ether was used and the only thing that is in favor is the fact that the organo-magnesium halide can be isolated from the solution free of ether.

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6. Organic Synthesis, Vol. XI pp. 84
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Malgren[5] makes the statement that a mixture of benzene and alkyl halide will not attack magnesium even on prolonged boiling. He believes that an ether solution must be present in order for the reaction to begin.

All the investigators[4] have found that if any solvent other than diethyl ether were used it was necessary to add heat to start the reaction and to keep it going.

In general, it has been found that the use of any solvents other than diethyl ether have not been satisfactory because heat is necessary to start and continue the reaction and also because poor yields are obtained.

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III. PREPARATION OF ANHYDROUS REAGENTS.

A. Drying of Diethyl Ether, Diisopropyl Ether and Butyl Ether.

Because the Grignard Reaction was inhibited considerably by the presence of water and alcohol, precaution was taken to make sure that they had been entirely removed. Since ordinary ethers contain some of the alcohol from which they are prepared, the ether was treated with anhydrous calcium chloride. This removed all the alcohol and most of the water. After standing for several days in contact with the calcium chloride, the ether was filtered off and fresh cut sodium was added. The sodium was allowed to remain in contact with the ether until no more bubbles of hydrogen were given off. The ether was then distilled. If the ether was not used immediately after distilling, it was advisable to add a few pieces of sodium and allow the ether to remain in contact with them.

B. Bromobenzene and Ethyl Benzoate.

The reagents were allowed to stand in contact with anhydrous calcium chloride for several days and then distilled.

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C. Magnesium.

The magnesium was placed in a desiccator for several days before it was to be used. This was usually long enough to completely dry it.

D. Bromopentane.

First it was necessary to prepare hydrobromic acid. This was done as follows: Twelve hundred grams of bromine were added to five hundred grams of water and fifteen hundred grams of crushed ice. This mixture was contained in a three-liter flask. Sulphur dioxide was then bubbled into the mixture and went below the surface of the bromine. The sulphur dioxide was allowed to bubble in for two or three hours and then the mixture was distilled at a temperature of 126° C.

This constant boiling point hydrobromic acid was then added to 300 grams of pentanol-2 and refluxed for several days. At the end of the period of refluxing the mixture was distilled at 127.9° C. It was then washed with sodium carbonate and dried over calcium chloride. As a precaution the bromopentane was distilled again.

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This constant boiling point hydrobromic acid was then added to 300 grams of pentanol-2 and refluxed for several days. At the end of the period of refluxing the mixture was distilled at 127.9° C. It was then washed with sodium carbonate and dried over calcium chloride. As a precaution the bromopentane was distilled again.

IV. DESCRIPTION OF PROCEDURE.

A. Triphenyl Carbinol.

After the reagents had been completely dried, 15 grams of bromobenzene were allowed to drop slowly onto 2.4 grams of magnesium turnings in 75 cc. of diethyl ether. A vigorous reaction started. However, in case the reaction was slow in starting, the flask containing the mixture was warmed by a steam bath. After the reaction had started, the remaining 35 grams of the bromobenzene were then added drop by drop. In case the reaction became too vigorous, the flask was cooled by immersing it in ice water. When the reaction had ceased, the flask was heated for 30 minutes on a water bath so that the ether gently boiled. The flask was then cooled and 75 cc. of ethyl benzoate in 50 cc. of anhydrous ether were added drop by drop. If, during the addition of the ethyl benzoate, the reaction became too vigorous, the flask was cooled with ice water. When all of the ethyl benzoate had been added, the mixture was gently heated on a steam bath for 15 minutes and then cooled. Small pieces of ice (150 grams), 8 cc. of dilute sulphuric acid were added and shaken until the magnesium complex had been entirely decomposed. The ether, excess reagents and by-products were removed by steam distillation.

IV. DESCRIPTION OF PROCEDURE.

A. Triphenyl Carbinol

After the reagents had been completely dried, 12 grams of bromobenzene were allowed to drop slowly onto 2.4 grams of magnesium turnings in 75 cc. of dethyl ether. A vigorous reaction started. However, in case the reaction was slow in starting, the flask containing the mixture was warmed by a steam bath. After the reaction had started, the remaining 75 grams of the bromobenzene were then added drop by drop. In case the reaction became too vigorous, the flask was cooled by immersing it in ice water. When the reaction had ceased, the flask was heated for 30 minutes on a water bath so that the ether gently boiled. The flask was then cooled and 75 cc. of ethyl benzoate in 50 cc. of anhydrous ether were added drop by drop. If, during the addition of the ethyl benzoate, the reaction became too vigorous, the flask was cooled with ice water. When all of the ethyl benzoate had been added, the mixture was gently heated on a steam bath for 15 minutes and then cooled. Small pieces of ice (150 grams), 5 cc. of dilute sulphuric acid were added and shaken until the magnesium complex had been entirely decomposed. The ether, excess reagents and by-products were removed by steam distillation.

The crude triphenyl carbinol which remained after the steam distillation was purified by recrystallization from alcohol or benzene. The theoretical yield is 12.85 grams.

B. Ethyl Magnesium Bromide and Pentyl Magnesium Bromide.

The method of preparing these reagents is very similar to that used in preparing phenyl magnesium bromide. The only difference being in the reagents used. In preparing ethyl magnesium bromide, ethyl bromide was the halogen compound used. In case of pentyl magnesium bromide the halogen compound was 1-bromopentane. Instead of carrying the procedure to completion, i.e., adding the carbonyl compound and hydrolyzing, the magnesium compound was hydrolyzed directly with standard acid. By knowing the amount of acid used and its normality, the weight of acid was computed and from this the weight of magnesium or halogen compound which had reacted.

As an example the case of hydrolyzing the ethyl magnesium bromide will suffice: HCl was the acid used.

(a) Normality of acid x cubic centimeters = milli equivalents.

(b) Milli equivalents x molecular weight of acid ÷ 1000 = weight of acid used.

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As an example the case of hydrolyzing the ethyl magnesium bromide will suffice: HCl was the acid used.

(a) Normality of acid x cubic centimeters = milli equivalents.

(b) Milli equivalents x molecular weight of acid $\div$ 1000 = weight of acid used.

(c) $Mg\begin{matrix}Br\\C_2H_5\end{matrix}$ + HCl $\longrightarrow$ $Mg\begin{matrix}Br\\Cl\end{matrix}$ + C_2H_6

y grams wt. found in (b)

M.W. = 133.24 M.W. = 36.5

(d) Mg + C_2H_5Br $\longrightarrow$ $Mg\begin{matrix}Br\\C_2H_5\end{matrix}$

x grams

M.W. = 24.32 M.W. = 133.24

It is seen that by direct proportion, the weight of magnesium or ethyl bromide which had reacted can be computed. In each case the efficiency was based upon the amount of magnesium used.

C. Discussion.

In preparing the several Grignard Reagents and using diisopropyl ether mixed with ethyl ether, it was necessary to add heat in all cases, both to start the reaction and to keep it going.

(c) $Mg(Br)C_2H_5$ + NCl ⟶ $Mg(Br)Cl$ + C_2H_5

y grams wt. found in (b)

M.W. = 132.24 M.W. = 36.5

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In preparing the several Grignard Reagents and using dilsopropyl ether mixed with ethyl ether, it was necessary to add heat in all cases, both to start the reaction and to keep it going.

V. COMPARISON OF YIELDS.

A. Preparation of triphenyl carbinol.

1. Using diethyl ether only.

Sample	$(C_2H_5)_2O$ used (cc.)	Yield (grs.)	% Eff.
1.	75	3.32	25.8
2.	75	4.06	31.6
3.	75	4.85	37.7
4.	75	5.90	45.8
5.	75	10.60	82.5

Remarks--- In Sample No. 5 mechanical stirring was used.

2. Using a mixture of diethyl ether and diisopropyl ether.

Sample	$(C_2H_5)_2O$ used (cc.)	$[(CH_3)_2CH]_2O$ used (cc.)	Yield (grs.)	% Eff.
1.	15	60	1.32	10.2
2.	15	60	1.77	13.7
3.	25	50	2.28	17.7
4.	40	40	2.54	19.7
5.	40	40	3.62	28.1
6.	40	40	3.44	26.7
7.	40	40	5.66	44.0

Remarks --- Heat was necessary in all cases.
In Sample No. 7 mechanical stirring was used.
2.4 Grams of magnesium was used in all cases.
Theoretical Yield of triphenyl carbinol = 12.85 grams.

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1.	15	60	1.32	10.2
2.	15	60	1.77	13.7
3.	25	50	2.26	17.7
4.	40	40	2.54	19.7
5.	40	40	3.02	23.3
6.	40	40	3.44	26.7
7.	40	40	5.56	44.0

Remarks --- Heat was necessary in all cases.
In Sample No. 7 mechanical stirring was used.
2.4 grams of magnesium was used in all cases.
Theoretical Yield of triphenyl carbinol = 12.65 grams.

B. Preparation of Ethyl Magnesium Bromide.

1. Using diethyl ether only.

Sample	$(C_2H_5)_2O$ used (cc.)	Grams of Magnesium reacted	% Eff.
1.	75	1.935	80.5
2.	75	2.03	84.6
3.	75	2.07	86.2

Remarks --- Mechanical mixing in all cases.

2. Using a mixture of diethyl ether and diisopropyl ether.

Sample	$(C_2H_5)_2O$ used (cc.)	$[(CH_3)_2CH]_2O$ used (cc.)	Grams of Magnesium reacted.	% Eff.
1.	40	40	0.696	29.0
2.	40	40	0.920	38.2
3.	40	40	0.838	34.9
4.	40	40	0.854	35.6

Remarks --- Mechanical mixing in all cases.

In Sample No. 3 external heating was necessary.

2.4 grams of magnesium used in all cases. In this preparation the Grignard Reagent was titrated with standard acid and the amount of magnesium which had reacted was computed.

B. Preparation of Ethyl Magnesium Bromide.

1. Using diethyl ether only.

Sample	$(C_2H_5)_2O$ used (cc.)	Grams of Magnesium reacted	% Eff.
1.	75	1.955	80.5
2.	75	2.05	84.6
3.	75	2.07	86.2

Remarks --- Mechanical mixing in all cases.

2. Using a mixture of diethyl ether and diisopropyl ether.

Sample	$(C_2H_5)_2O$ used (cc.)	$(CH_3)_2CH]_2O$ used (cc.)	Grams of Magnesium reacted.	% Eff.
1.	40	40	0.696	29.0
2.	40	40	0.920	38.2
3.	40	40	0.858	34.9
4.	40	40	0.854	35.6

Remarks --- Mechanical mixing in all cases.

In Sample No. 3 external heating was necessary.

2.4 grams of magnesium used in all cases. In this preparation the Grignard Reagent was titrated with standard acid and the amount of magnesium which had reacted was computed.

C. Preparation of Pentyl Magnesium Bromide.

1. Using butyl ether only.

Sample	Butyl ether used (cc.)	Grams of Magnesium reacted.	% Eff.
1.	50	2.09	41.7
2.	75	6.14	61.4
3.	75	5.43	54.3
4.	75	6.92	69.2

Remarks: (1) Mechanical stirring in all cases.

(2) In run No. 1 5.0 grams of magnesium were used.
In all other runs 10 grams were used.

(3) The Grignard Reagent formed in all cases was titrated with standard acid and the amount of magnesium which reacted was computed.

2. Using diisopropyl ether only.

Sample	Diisopropyl ether used (cc.)	Grams of Magnesium reacted.	% Eff.
1.	73	1.28	25.7
2.	57	1.11	22.2
3.	60	1.16	23.2
4.	76	0.98	19.8
5.	79	0.86	17.3
6.	48	1.19	23.8
7.	50	2.64	26.4
8.	50	2.41	24.1

D. Preparation of Ethyl Magnesium Bromide.

1. Using butyl ether only.

Sample	Butyl ether used (cc.)	Grams of Magnesium reacted.	% Eff.
1.	55	2.09	41.7
2.	75	6.14	61.4
3.	75	5.43	54.3
4.	75	6.92	69.2

Remarks: (1) Mechanical stirring in all cases.

(2) In run No. 1 2.0 grams of magnesium were used.
In all other runs 10 grams were used.

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Sample	Diisopropyl ether used (cc.)	Grams of Magnesium reacted.	% Eff.
1.	75	1.26	25.7
2.	57	1.11	22.2
3.	60	1.16	23.2
4.	76	0.98	19.8
5.	79	0.86	17.3
6.	46	1.19	23.8
7.	50	2.64	26.4
8.	50	2.41	24.1

Remarks: (1) Mechanical stirring and heat used in all cases.

(2) In runs Nos. 1-6 five grams of magnesium were used. In 7 and 8 ten grams were used.

(3) Titration as in Remarks C 1 (3).

3. Using a mixture of butyl ether and siisopropyl ether.

Sample	Butyl ether used (cc.)	Diisopropyl ether used (cc.)	Grams of Magnesium reacted.	% Eff.
1.	25	25	3.27	32.7
2.	25	35	3.03	30.3
3.	35	25	3.19	31.9
4.	50	25	4.23	42.3

Remarks: (1) Mechanical stirring and heat used in all cases.

(2) Ten grams of magnesium used in all cases.

(3) Butyl ether added at the beginning and when the reaction had started the diisopropyl ether was added slowly.

(4) Titration as in Remark C 1 (3).

Remarks: (1) Mechanical stirring and heat used in all cases.

(2) In runs Nos. 1-6 five grams of magnesium were used. In 7 and 8 ten grams were used.

(3) Titration as in Remarks 0 1 (3).

3. Using a mixture of butyl ether and diisopropyl ether.

Sample	Butyl ether used (cc.)	Diisopropyl ether used (cc.)	Grams of Magnesium reacted.	% Eff.
1.	25	25	3.27	32.7
2.	25	35	3.03	30.3
3.	35	25	3.17	31.9
4.	30	25	4.25	42.5

Remarks: (1) Mechanical stirring and heat used in all cases.

(2) Ten grams of magnesium used in all cases.

(3) Butyl ether added at the beginning and when the reaction had started the diisopropyl ether was added slowly.

(4) Titration as in Remark 0 1 (3).

VI. SUMMARY

As a result of the research done recently, using diisopropyl ether as a solvent for Grignard Reagents, a few conclusions can be stated briefly.

(1) It was found that diisopropyl ether can be used as a solvent in preparing Grignard Reagents.

(2) That although diisopropyl ether can be used the yield of the product is greatly reduced. It was found that, using diethyl ether alone, the yield of triphenyl carbinol was 4.54 grams. This is 35.3% of the theoretical yield. In using a 50-50 mixture of diethyl ether and diisopropyl ether in preparing the same compound, the yield was reduced to 3.18 grams or 24.7% of the theoretical. Using 60 cc. of diisopropyl ether and 15 cc. of diethyl ether, the yield was reduced still further giving 1.54 grams or 12.0% of the theoretical.

In preparing ethyl magnesium bromide, and using diethyl ether alone, the yield was 83.8% of the theoretical and using a 50-50 mixture of diisopropyl ether and diethyl ether, the yield was reduced to 34.4% of the theoretical.

In preparing n-pentyl bromide, the average yield using butyl ether alone was 56.6% of the theoretical. Using diisopropyl ether alone the average yield was 22.8% of the theoretical. In preparing triphenyl carbinol and ethyl magnesium bromide, the reaction between the halogen compound

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In preparing n-pentyl bromide, the average yield using butyl ether alone was 56.6% of the theoretical. Using diisopropyl ether alone the average yield was 22.8% of the theoretical. In preparing triphenyl carbinol and ethyl magnesium bromide, the reaction between the halogen compound

and the magnesium would not start using diisopropyl ether alone. In preparing n-pentyl magnesium bromide, a catalyst [I] was used and this was enough to start the reaction although heat had to be added when only a small portion of the diisopropyl ether had been added. Using a 50-50 mixture the average yield was 34.3% of the theoretical.

(3) It was found that the reaction would not continue without the addition of heat after 1.6 times as much isopropyl ether had been added to the volume of diethyl ether already present. At this point the reaction was continuing at a very slow rate.

(4) It was found that the addition of heat and the use of a mechanical stirrer greatly increased the yield. In preparing triphenyl carbinol and using diethyl ether alone a yield of 10.60 grams was obtained and using a 50-50 mixture of diisopropyl ether and diethyl ether the yield was 5.66 grams.

and the magnesium would not start using diisopropyl ether alone. In preparing n-pentyl magnesium bromide, a catalyst [I] was used and this was enough to start the reaction although heat had to be added when only a small portion of the diisopropyl ether had been added. Using a 30-30 mixture the average yield was 94.3% of the theoretical.

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